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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/177,387	10/23/98	HARTLEY J	0942.2850004

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STERNE KESSLER GOLDSTEIN & FOX
1100 NEW YORK AVENUE NW
SUITE 600
WASHINGTON DC 20005-3934

EXAMINER	
YUCEL, I	
ART UNIT	PAPER NUMBER
1636	26

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary	Application No. 09/177,387	Applicant(s) HARTLEY ET AL.	
	Examiner Yucel Remy	Art Unit 1636	

-- The MAILING DATE of this communicati n appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 July 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26,28-35,52 and 89-117* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26,28-35,52 and 89-99* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

DETAILED ACTION

Claims 26, 28-35, 52, and 89-117 are pending in the application. This Office action is in response to the amendment filed 25 July 2001.

Response to Amendment

The amendment filed 25 July 2001 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: "wherein at least one of said first and second recombination sites comprises one or more mutations that enhance recombination specificity."

Applicant indicates page 23, lines 14-19, pages 41-44 and the examples as providing support for said amendment. Page 23, lines 14-19 are directed to enhancing production of products. It is not clear if "products" refers to the protein/polypeptides produced as a result of expression of nucleic acids that have undergone site-specific recombination mediated by a recombinase or to the nucleic acids. In any event, "enhancing production of products" is not the equivalent of "enhancing specificity of recombination." Therefore, this passage of the specification does not provide adequate support for the amendment.

Pages 41-44 describe mutations that enhance site specific recombination and the different measures of enhancement. Some mutations remove stop codons, allowing for enhanced expression or production of fusion proteins (see page 41). The specification does not explicitly teach that such mutation affect recombination

specificity. The disclosure, rather teaches mutations which may enhance transcription and/or translation efficiency--without changing the specificity of recombination. The balance of the pages describes general methods in which mutations are introduced into recombination sites.

A survey of the examples presented in the specification fails to reveal how recombination specificity is enhanced. Examples 1 and 2 are drawn to the use of loxP sites, which are excluded from the present claims. Example 3 is directed to the use of mutant attB sites that have stop codons removed, but the data do not indicate that recombination specificity has been enhanced as a result of the mutation. Example 4 describes another mutation that prevents hairpin formation. As discussed immediately above, the data do not illustrate that recombination specificity has been enhanced. None of the remaining examples appear to demonstrate increased recombination specificity attributable to the mutant recombination sites used. Applicant is encouraged to indicate those portions of the specification that clearly provide support for increased or enhance recombination specificity.

Applicant is required to cancel the new matter in the reply to this Office Action.

The rejection of claims 26, 28-35, 52, 89-93, 98 and 99 under U.S.C. § 102(b) as being anticipated by Bebee et al. (hereinafter "Bebee") has been withdrawn in favor of the new ground of rejection presented below.

The rejection of claims 26, 28-35, 52, 89-96, 98 and 90 under 35 U.S.C. § 103(a) as being unpatentable over either Kilby or Snaith in view of Ausubel in further view of

Padget or Grose and Hall and Baum has been withdrawn in light of Applicant's amendments.

The rejection of claims 94-96 under 35 U.S.C. § 103(a) as being unpatentable over Bebee in view of Hall has been withdrawn in light of Applicant's amendments.

The rejection of claims 90 and 96 under 35 U.S.C. §112, second paragraph has been withdrawn in light of Applicant's amendments.

Claims 26, 28-35, 52, 98 and 99 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Bebee et al. in view of Schlake for the reasons presented below.

Claims 26, 28-35 and 52 stand rejected under U.S.C. § 103(a) as being unpatentable over Shuman in view of Schlake for the reasons presented below.

Claims 26, 28-35, 52 and 89-99 stand rejected under 35 U.S.C. § 112, first paragraph new matter and written description for the reasons presented below.

Allowable Subject Matter

Claims 100-117 are allowable over the prior art.

New Grounds of Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 26, 28-35, 52, 98 and 99 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bebee et al. (US patent 5,434,066, hereinafter "Bebee") in view of Schlake et al. (Biochemistry, 1994, 33:12746-12751).

The instant claims are drawn to methods in which mutant recombination sites that enhance recombination specificity are attached to a double stranded nucleic acid molecule through the use of primers with sequences which comprise said sites and an enzyme with polymerase activity.

Bebee et al. teach cloning of nucleic acids (DNA) by taking advantage of site-specific recombination systems. At column 4, beginning at line 56 they teach that their method requires that the target sequence has sites that are recognized by the recombinase being used and that the method, therefore, does not rely upon the presence of restriction sites to achieve the desired cloned product(s). They teach that the sites may be naturally present at the termini of a linear molecule but will more commonly be added to the target sequence via ligation or primer extension (i.e. the instant methods). At columns 5-7, Bebee et al. teach several "site-specific" recombinase systems which are suitable for their methods. They identify several preferred embodiments including Int, Int/Xis, Cre, transposons, Tn3 resolvase, Flp, Hin and Cin as suitable for their recombinase based methods of cloning. These systems (and therefore the recombination sites) are exactly those recited by the instant claims.

Applicant's attention is also drawn to column 9 where Bebee et al. discuss various att sites.

Bebee et al. further illustrate how primer extension methods are used to incorporate recombination sites into a target nucleic acid molecule. They teach the sequences for the specific lox P sites recognized by the Cre enzyme (see for example column 5). They also teach PCR primers #790 and #791 that include the loxP recombination sites and the amplification of a kanamycin resistance gene from a plasmid with said primers. They teach that as a result of PCR, a "cassette" or fragment comprising the kanamycin resistance gene flanked by loxP sites is obtained (see for example, columns 11 and 12). They further teach that this product (cassette) was ligated into another construct, indicating that as a result of PCR amplification, a double-stranded product was obtained. Bebee et al. do not specifically disclose specific thermostable DNA polymerases used in their PCR reactions; however, the list recited in claim 33 is fairly complete and recites some of the first commercially available enzymes such as Taq, VENT and DEEPVENT. That Bebee et al. did not specify the polymerase used in their PCR reaction indicates that any DNA polymerase suitable for PCR would be appropriate in their methods and that by the time of their invention, PCR protocols were well known and established to the point that one of ordinary skill in the art would have recognized and known appropriate DNA polymerases (thus Bebee et al. did not need to disclose that which was well known).

Schlake teaches the generation of mutated FLP recognition target (FRT) sites for the introduction of expression cassettes at defined locations. Using different

combinations of mutated and wildtype sites, the methods taught by Schlake allow manipulation of the types of recombination events that occur (see abstract, for example). The mutant sites further allow simultaneous individual recombination events to occur without the use of additional different types of recombinases. The protocols taught by Schlake result in certain recombination events over others, thus, read on the newly added recitation of "enhanced recombination specificity."

The ordinary artisan would have been motivated to modify the methods taught by Bebee to include modified or mutated recombination sites as exemplified by Schlake to control or favor certain recombination events over others and to perform simultaneous recombination events using a single recombinase. The ordinary artisan would have had an expectation of success because of the teachings of Schlake that illustrate that mutated recombination sites allow one to favor certain recombination events over others and to achieve several recombination events simultaneously. Therefore, the present invention would have been obvious to one of ordinary skill in the art at the time it was made.

Claims 26, 28-35 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shuman (U.S. Patent 5,766,891, hereinafter "Shuman") in view of Schlake.

The claims have been described above. Shuman teaches construction of chimeric nucleic acid molecules in vitro using the site-specific recombinase from Vaccinia virus. Shuman teaches that this enzyme cleaves at a consensus pyramidine

element (see for example column 1). At column 6, Shuman teaches how nucleic acids are cloned using his system. He teaches the construction of bivalent nucleic acid substrates that are duplex molecules flanked by the recognition sequences for the Vaccinia (topoisomerase) recombinase enzyme. Shuman explicitly teaches the addition of the recombination sites via a primer extension method (see for example lines 46-55). He further explains this procedure at column 7, second full paragraph. Shuman clearly teaches the production of nucleic acids to be cloned which comprise recombination sites at one or both ends wherein said sites are added via a primer extension method. Schlake teaches the generation of mutated FLP recognition target (FRT) sites for the introduction of expression cassettes at defined locations. Using different combinations of mutated and wildtype sites, the methods taught by Schlake allow manipulation of the types of recombination events that occur (see abstract, for example). The mutant sites further allow simultaneous individual recombination events to occur without the use of additional different types of recombinases. The protocols taught by Schlake result in certain recombination events over others, thus, read on the newly added recitation of "enhanced recombination specificity."

The ordinary artisan would have been motivated to modify the methods taught by Shuman to include modified or mutated recombination sites as exemplified by Schlake to control or favor certain recombination events over others and to perform simultaneous recombination events using a single recombinase. The ordinary artisan would have had an expectation of success because of the teachings of Schlake that illustrate that mutated recombination sites allow one to favor certain recombination

events over others and to achieve several recombination events simultaneously. Therefore, the present invention would have been obvious to one of ordinary skill in the art at the time it was made.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26, 28-25, 52, and 89-99 are rejected under 35 U.S.C. 112, first paragraph, (new matter) as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

As discussed above, the amendment filed 25 July 2001 is objected to because it contains new matter. The portions of the specification Applicant indicates as providing support for enhancing "recombination specificity" refer instead to enhanced product production (which may not have any connection to a level of recombination specificity). According to Applicant's disclosure, removal of stop codons and sequences involved in hairpin formation are examples of mutations that result in enhanced product production. However, no link can be drawn between these mutations and "recombination specificity"

based on Applicant's specification. As such, the recitation of enhanced "recombination specificity" constitutes new matter and must be removed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 26, 28-35, 52 and 89-99 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Because Applicant has not provided an adequate definition of the term "enhance[d] recombination specificity," it is not clear what is embraced by the claims. The claims are rendered vague and indefinite because their metes and bounds cannot be established.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Remy Yucel, Ph.D. whose telephone number is (703) 305-1998. The examiner can normally be reached on Monday-Friday, 8:00am-4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached at (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-7939 for regular communications and (703) 305-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to patent analyst Dianiece Jacobs whose telephone number is (703) 305-3388.

Remy Yucel, Ph.D.
Primary Examiner
Art Unit 1636

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October 9, 2001